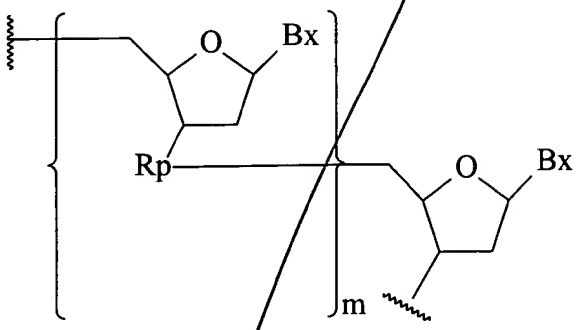


wherein:

each Rp is a chiral Rp phosphorothioate internucleotide linkage; and

each n, m and p is, independently, from 1 to 100; where the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12}, R_{13}, R_{14} and Lx is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage.

43. (Amended) A pharmaceutical composition comprising a compound of claim 23 and an acceptable pharmaceutical carrier.

Please cancel the second occurrence of claim 3 and replace it with new claim 44:

44. (New) The oligomeric compound of claim 2 wherein each nucleoside in the external regions comprises a substituent group.

REMARKS

Claims 1-43 are pending in the instant application. Claims 23 and 43 have been amended. New claim 44 has been added as a replacement for the second occurrence of claim 3.

The Office Action includes rejections under 35 U.S.C. §§ 102(b), 103(a), and 112, second paragraph, as well as under the judicially created doctrine of obviousness-type double patenting. In view of the remarks to follow, Applicants request that these rejections be reconsidered and withdrawn.

Obvious-Type Double Patenting

Claims 1-14 and 17-43 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 9 of commonly owned U.S. Patent No. 5,852,188. Applicants request that this rejection be deferred pending some identification of allowable subject matter, as it likely can be readily resolved (depending upon the subject matter ultimately allowed) through the filing of a suitable terminal disclaimer.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

The definiteness of a claim is evaluated in the context of whether its scope is clear to a hypothetical skilled person in the pertinent art. MPEP § 2171 at 2100-144. The Office Action asserts that claims 1-8 and 15-22 are indefinite because Applicants "[have] not set forth what moieties or compounds encompass/define the external region" (Office Action at 2). In response, Applicants respectfully submit that those skilled in the art would recognize that, by its plain meaning, the "external region" as recited in claim 1, for example, is any compound connected to either side of the chiral phosphorothioate-linked internal region. Significantly, claim 1, for example, recites an oligomeric compound having an internal region that is defined by R_p chiral phosphorothioate linked 2'- deoxynucleosides and that such internal region is "flanked" by two "external regions" of linked nucleoside or nucleosides. Thus, by the plain and ordinary language of claim 1, the two flanking external regions of linked nucleoside or nucleosides are not linked by R_p chiral phosphorothioate linkages, thereby distinguishing the "external regions" from the "internal region." Moreover, Applicants' specification defines two external regions at pages 27-28 and exemplifies oligomeric compounds according to Applicants' claimed invention at pages 75-76 (Table I). Indeed, one skilled in the art would not have difficulty determining the meaning or scope of the "external region" as used in Applicants claims.

It is also asserted that claims 9-14 are vague and indefinite because the position of the attachment of the substituents relative to the external region are not defined. Applicants

respectfully submit, however, that Applicants' do not intend to limit the position of the attachment of the substituents in the external region, nor do the patent laws require Applicants to do so, as long as the external region imparts nuclease resistance to the claimed oligomeric compounds. Indeed, those skilled in the art would readily be able to determine whether particular substituents attached to the external regions would impart nuclease resistance to the external regions of claimed oligomeric compounds. Thus, since those skilled in the art would not have any difficulty determining whether an oligomeric compound is or is not within the scope of the claims, the claims are definite within the meaning of the patent laws. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims). Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, are respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

1. *U.S. Patent No. 5,883,237 to Stec et al. ("the Stec patent")*

Claims 1-4, 7, 8, 11-13, and 17-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Stec patent. Applicants respectfully traverse this rejection because the Stec patent does not disclose each and every claim element. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ.2d 1051, 1053 (Fed. Cir. 1987) ("A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.").

Applicants' claimed invention relates to oligomeric compounds comprising a plurality of covalently-bound nucleosides wherein the oligomeric compound has an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region, wherein the external regions impart nuclease resistance to the oligomeric compound (*see, e.g.*, claim 1).

The Stec patent, in contrast, does not disclose an oligonucleotide having an **internal region** of Rp chiral phosphorothioate linked 2'-deoxynucleosides **and two external regions**

flanking said internal region. Although the Office Action asserts that the Stec patent teaches the recited characteristic at column 7, lines 14-67 (Office Action at 2-3), the Stec patent merely discloses solid phase synthesis of a polymer having a predetermined sequence of R_p or S_p linkages (*see, e.g.*, col. 2, lines 56-61). Nowhere does the Stec patent teach an oligonucleotide having **3 regions**: (1) an internal region of R_p chiral phosphorothioate linkages; and (2) & (3) two external regions **flanking** the internal region. Indeed, column 7, lines 14-67 confirms this: the only sequences disclosed in the cited passage of the Stec patent are either all "ps," all "pr," or alternating "ps" and "pr" linkages (col. 7 at lines 41-43). Thus, the Stec patent does not disclose "**an internal region** of Rp chiral phosphorothioate linked 2'-deoxynucleosides and **two external regions flanking** said internal region" as recited in Applicants' claimed invention. Accordingly, the Stec patent does not disclose every element of Applicants' claimed invention and, thus, cannot anticipate any of the above-identified claims.

2. *U.S. Patent No. 5,506,212 to Hoke et al. ("the Hoke patent")*

Claims 1-4, 6-8, 11-13, and 17-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Hoke patent. Applicants respectfully traverse this rejection because the Hoke patent does not disclose each and every claim element.

The Hoke patent does not disclose an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region. Although the Office Action asserts that the Hoke patent teaches the recited characteristic at columns 7-9 and claims 2 and 4 (Office Action at 3), Applicants cannot find any such teaching in the Hoke patent. Rather, the Hoke patent appears to relate to sequence-specific phosphorothioate oligonucleotides having ***substantially chirally pure*** intersugar linkages. This neither discloses nor suggests "an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions **flanking** said internal region" as recited in Applicants' claimed invention. Accordingly, the Hoke patent does not disclose every element of Applicants' claimed invention and, thus, cannot anticipate any of the above-identified claims.

3. *U.S. Patent No. 5,852,188 to Cook ("the Cook patent")*

Claims 1-14 and 17-43 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by the Cook patent. Applicants respectfully traverse this rejection because the Cook patent does not disclose each and every claim element.

The Cook patent does not disclose an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region. Although the Office Action asserts that the Cook patent teaches the recited characteristic at column 5, line 45 – column 7 (Office Action at 3-4), Applicants note that no such teaching is present in the Cook patent. Rather, the Cook patent discloses sequence-specific oligonucleotides having either **substantially pure** or **pure** chiral Sp phosphorothioate, chiral Rp phosphorothioate, chiral Sp alkylphosphonate, chiral Rp alkylphosphonate, chiral Sp phosphoamidate, chiral Rp phosphoamidate, chiral Sp phosphotriester, and chiral Rp phosphotriester linkages (*see, e.g.*, col. 5, lines 46-67). Since the Cook patent does not disclose the structure recited in the present claims, the Cook patent cannot anticipate the same.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) are respectfully requested.

Rejection Under 35 U.S.C. § 103

Claims 1-4, 6-14, 17-21, and 24-42 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Cook patent (above) in combination with U.S. Patent No. 5,532,130 to Alul ("the Alul patent"). Applicants respectfully request that this rejection be withdrawn, as there is no evidence of record indicating that those of ordinary skill would have been motivated to combine the teachings of the Cook and the Alul patents or even that such combination would result in Applicants' claimed invention. Indeed, such combination is ***not*** a combination that those of ordinary skill in the art would have been motivated to make at the time Applicants' invention was filed.

Applicants' claimed invention relates to oligomeric compounds comprising a plurality of covalently-bound nucleosides wherein the oligomeric compound has **an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said**

internal region, wherein the external regions impart nuclease resistance to the oligomeric compound (*see, e.g.*, claim 1). Thus, the oligomeric compounds Applicants' claimed invention are defined as having, *inter alia*,

(1) an internal region of Rp chiral phosphorothioate;

(2) linked **2'-deoxy**nucleosides; and

(3) two external regions flanking said internal region (Id.).

The combination of the Cook and Alul patents would **not** produce **even one of the above-listed elements**. As discussed above, the Cook patent does not disclose "an internal region of Rp chiral phosphorothioate linked 2'-deoxynucleosides and two external regions flanking said internal region" as recited in Applicants' claimed invention (elements 1 and 3, above).

Moreover, Applicants' claims do not require a 2',5' internucleoside linkage within the oligonucleotide compound as indicated at page 6 of the Office Action:

> [a]lthough Cook does not teach the presence of a 2',5' internucleoside linkage within the oligonucleotide compound, Alul teaches that 2'-5' linkages confer resistance to both exo and endonucleolytic degradation . . . .

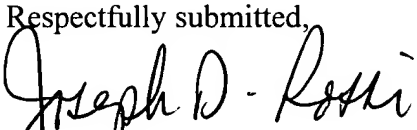
Rather, Applicants' claims require an oligomer that includes **2'-deoxynucleosides**, i.e., a nucleosides that have a **2'-deoxy position**. Significantly, the "2'-" in Applicants' claims does not refer to the position of the linking moiety. Thus, the combination of the Cook and Alul patents would not have resulted in the linked **2'-deoxy**nucleosides that are recited in Applicants' claims. Since one skilled in the art would recognize that the combination of the Cook and Alul patents would not yield Applicants claimed invention, the proposed modification would ***not*** have been one that those of ordinary skill would have been motivated to make at the time Applicants' patent application was filed. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Applicants respectfully submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested.

Respectfully submitted,



Joseph D. Rossi
Registration No. **47,038**

Date: August 7, 2002
WOODCOCK WASHBURN LLP
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the application as follows:

In the Specification:

Please replace the paragraph on page 1, beginning at line 5, with the following replacement paragraph:

--This patent application is a continuation-in-part of Application Serial No. [09/325,058] 09/352,058, filed on July 14, 1999, entitled "Oligonucleotides Having Site Specific Chiral Phosphorothioate Internucleoside Linkages", the contents of which is incorporated herein by reference in its entirety.--

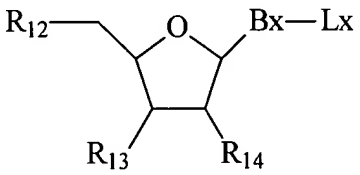
Please replace the paragraph on page 16, beginning at line 7, with the following replacement paragraph:

-- In a preferred embodiment the oligomeric compounds of the invention have the formula:

$$5'\text{-}(Nu_1\text{-}L_1)_n\text{-}Y\text{-}(L_2\text{-}Nu_2)_p\text{-}3'$$

wherein:

each Nu_1 and Nu_2, independently, has the formula:



wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R_{12}, R_{13} and R_{14} is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

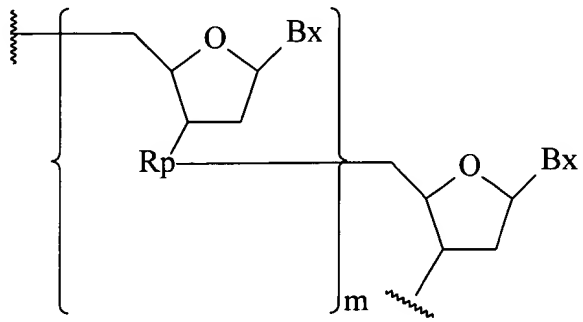
another of R_{12}, R_{13} and R_{14} is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R_{12}, R_{13} and R_{14} of Nu_1, is L_1;

the remaining of R_{12}, R_{13} and R_{14} of Nu_2, is L_2;

each L_1 and each L_2 is, independently, a phosphodiester internucleoside linkage or a modified internucleoside linkage;

Y has the formula:



wherein:

each Rp is a chiral Rp phosphorothioate internucleotide linkage; and

each n, m and p is, independently, from 1 to 100; where the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12}, R_{13}, R_{14} and Lx is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage.--

Please replace the paragraph on page 84, beginning at line 11, with the following replacement paragraph:

-- SEQ ID NO: 5 was used in a comparative study to [determin] <u>determine</u> the effect of chiral internucleotide linkages at predetermined positions compared to the same sequence having racemic linkages at each position. The capillary gel electrophoretic analysis indicated the relative

nuclease resistance of Chiral 3'-Sp- capped oligomers compared to ISIS 3082 (XVI,uniform 2'-deoxy phosphorothioate). Because of the resistance of Sp linkage to nucleases, Compounds XVII and XVIII are found to be stable in plasma, kidney and liver while XVI (3082) is not. On the other hand, the data from 5',-3'-bis Sp capped oligomers show total exonucleolytic stability in plasma as well as in tissues (liver and kidney). Compounds are stable at various time points such as 1, 3, and 24 hours. The fact that no degradation is detected proved that 5'-exonucleases and 3'-exonuclease are prevalent in tissues and endonucleases are not active. Furthermore, a single chiral linkage (Sp thioate linkage) is sufficient as a gatekeeper against nucleases at the termini.--

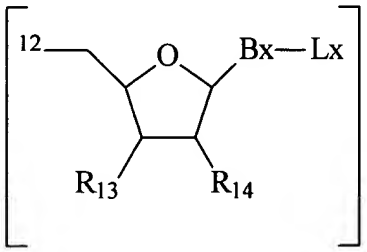
In the Claims:

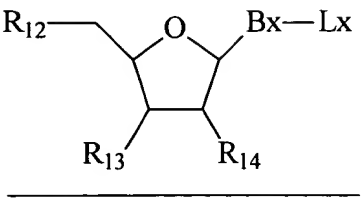
23. (Amended) An oligomeric compound of the formula:

$$5'\text{-}(Nu_1\text{-}L_1)_n\text{-}Y\text{-}(L_2\text{-}Nu_2)_p\text{-}3'$$

wherein:

each Nu_1 and Nu_2, independently, has the formula:





wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R_{12}, R_{13} and R_{14} is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

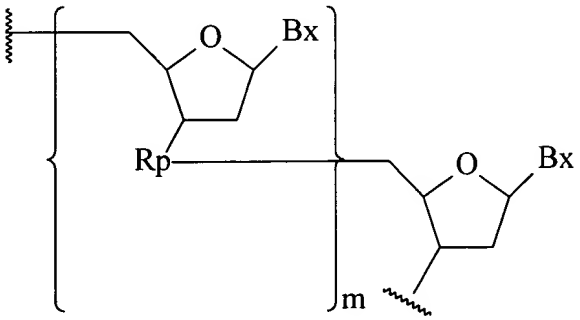
another of R_{12}, R_{13} and R_{14} is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R_{12}, R_{13} and R_{14}, of Nu_1, is L_1;

the remaining of R_{12}, R_{13} and R_{14}, of Nu_2, is L_2;

each L_1 and each L_2 is, independently, a phosphodiester internucleoside linkage or a modified internucleoside linkage;

Y has the formula:



wherein:

each Rp is a chiral Rp phosphorothioate internucleotide linkage; and

each n, m and p is, independently, from 1 to 100; where the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12}, R_{13}, R_{14} and Lx is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage.

43. (Amended) A pharmaceutical composition comprising a compound of claim [1] 23 and an acceptable pharmaceutical carrier.

Please cancel the second occurrence of claim 3 and replace it with new claim 44:

--44. (New) The oligomeric compound of claim 2 wherein each nucleoside in the external regions comprises a substituent group.--